An Observational Study of the Equivalence of Age and Duration of Diabetes to Glycemic Control Relative to the Risk of Complications in the Combined Cohorts of the DCCT/EDIC Study

*Ionut Bebu,[1] Barbara H. Braffett,[1] David Schade,[2] William Sivitz,[3] John I. Malone,[4] Rodica Pop-Busui,[5] Gayle M. Lorenzi,[6] Pearl Lee,[5] Victoria R. Trapani,[1] Amisha Wallia,[7] William H. Herman,[5] and John M. Lachin,[1] on behalf of the DCCT/EDIC Research Group**

Diabetes Care 2020;43:2478–2484 | https://doi.org/10.2337/dc20-0226

EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

This epidemiological analysis of the pooled Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort describes the equivalence of a 1-percentage point increase in HbA_{1c} (such as from 7% to 8%) and years of additional age or duration of type 1 diabetes (T1D) relative to the risk of complications.

RESEARCH DESIGN AND METHODS

Separate Cox proportional hazards models determined the number of additional years of age and/or duration of T1D that would result in the same increase in risk of microvascular (retinopathy, nephropathy, and neuropathy) and cardiovascular complications and mortality as a 1-percentage point increase in HbA_{1c}.

RESULTS

The risk of any cardiovascular disease associated with a 1-percentage point increase in HbA_{1c} was equivalent to the risk associated with 4.3 (95% CI 2.7–5.9) additional years of age or 5.6 (95% CI 2.7–6.5) additional years' duration of T1D. The risk of estimated glomerular filtration rate <60 mL/min/1.73 m^2 and/or end-stage renal disease associated with a 1-percentage point increase in HbA_{1c} was equivalent to the risk associated with 12.1 (95% CI 8.3–15.9) additional years of age or 18.0 (95% CI 4.3–31.7) additional years' duration of T1D. The proliferative diabetic retinopathy risk associated with a 1-percentage point increase in HbA_{1c} was equivalent to the risk associated with 6.4 (95% CI 5.3–7.4) additional years' duration of T1D, while for mortality risk, it was equivalent to the risk associated with 12.9 (95% CI 6.6–19.3) additional years of age.

CONCLUSIONS

Our results help evaluate the impact of glycemia on advanced complications in a way that may be more interpretable to health care providers and individuals with T1D.

[1]Biostatistics Center, The George Washington University, Rockville, MD
[2]The University of New Mexico, Albuquerque, NM
[3]The University of Iowa, Iowa City, IA
[4]University of South Florida, Tampa, FL
[5]University of Michigan, Ann Arbor, MI
[6]University of California, San Diego, La Jolla, CA
[7]Northwestern University, Evanston, IL

Corresponding author: Ionut Bebu, ibebu@bsc.gwu.edu

Received 31 January 2020 and accepted 13 July 2020

Clinical trial reg. nos. NCT00360893 and NCT00360815, clinicaltrials.gov

**A complete list of the investigators and members of the DCCT/EDIC Research Group can be found in N Engl J Med 2017;376:1507–1516.*

Individuals with type 1 diabetes (T1D) are at increased risk of microvascular and cardiovascular complications compared with the general population without diabetes (1–3). While mortality also has been historically higher in this vulnerable population, more recent findings are mixed (3–7).

The Diabetes Control and Complications Trial and its observational follow-up study, the Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC), demonstrated that hyperglycemia is a major risk factor for vascular complications and mortality in individuals with T1D, as are age and/or longer duration of T1D (8–10). In this study, we describe the effects of average glycemia on the risk of adverse outcomes in terms of an equivalent number of additional years of age or T1D duration. We have performed analyses for microvascular (retinopathy, nephropathy, and neuropathy) complications and cardiovascular disease (CVD) as well as mortality.

We previously showed that older age and hyperglycemia are associated with increased risk of CVD in DCCT/EDIC (11). Since better glycemic control decreased the risk of CVD, then at any year of age (e.g., 50 years), an individual with a higher HbA_{1c} level (for example, of 8%) would have a higher risk of CVD than a same-aged individual with an HbA_{1c} level of 7%. We now estimate how many additional years of age would be required for the participant with the HbA_{1c} level of 7% to reach the same level of CVD risk as the participant with the HbA_{1c} level of 8%. In this article, we have expressed the effect of a 1-percentage point increase in HbA_{1c} (e.g., from 7% to 8%) on the risk of microvascular and CVD complications and mortality in the number of years of age that would yield the same increase in risk of CVD (i.e., same log hazard ratio [HR]). Likewise analyses were then conducted for duration of T1D instead of age.

RESEARCH DESIGN AND METHODS

Participants

The methods of the DCCT/EDIC study have been previously described in detail (12,13). Briefly, the DCCT enrolled 1,441 individuals with T1D who were then randomly assigned to receive either intensive therapy ($n = 711$) or conventional therapy ($n = 730$). Intensive therapy aimed to achieve glycemic levels as close to normal as safely possible, while conventional therapy aimed to prevent symptoms of hypo- and hyperglycemia with no predefined glycemic targets. In 1993, after a mean follow-up of 6.5 years, the DCCT ended. All participants were taught intensive therapy and referred to their health care providers for their diabetes care. In 1994, the observational follow-up study, EDIC, enrolled 96% of the surviving DCCT cohort, with 94% of the surviving DCCT cohort still actively participating after >20 years since the start of EDIC.

The present analyses used all available data in the full cohort ($n = 1,441$) over the combined DCCT/EDIC follow-up.

Risk Factors

HbA_{1c} was measured quarterly during DCCT and annually during EDIC using high-performance liquid chromatography. To account for the different measurement frequencies during DCCT and EDIC, the models used the mean updated DCCT/EDIC HbA_{1c}, which is a time-dependent exposure calculated by weighting each value by the time interval between measurements (one-quarter over quarterly DCCT follow-up and one over annual EDIC follow-up) (14). The DCCT baseline HbA_{1c} value was not included in the calculation of the mean updated DCCT/EDIC HbA_{1c} value.

Cardiovascular Outcomes

Annual medical histories and electrocardiograms were used to ascertain CVD events. A committee masked to DCCT treatment group and HbA_{1c} levels adjudicated all CVD events based on documentation provided in external medical records. The composite CVD outcome was defined as time to the first occurrence of CVD death, nonfatal myocardial infarction (MI), nonfatal stroke, subclinical MI on electrocardiogram (silent MI), angina confirmed by ischemic changes with exercise tolerance testing or by clinically significant obstruction documented on coronary angiography, revascularization (with angioplasty or coronary artery bypass), or congestive heart failure (paroxysmal nocturnal dyspnea, orthopnea, or marked limitation of physical activity caused by heart disease). Major adverse cardiovascular events (MACE) included CVD death, nonfatal MI, or nonfatal stroke (8,11).

Renal Assessments and Outcomes

From DCCT baseline through EDIC year 18 (2012), albumin excretion rate (AER) was measured from 4-h urine samples using fluoroimmunoassay. In EDIC year 19, spot urine samples were collected, and AER was estimated using the ratio of urine albumin and urine creatinine concentrations. Serum creatinine was measured annually. Serum creatinine levels, age, sex, and race were used to calculate the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation. End-stage renal disease was defined as the initiation of maintenance dialysis or kidney transplantation assessed yearly by questionnaire and adjudicated centrally. Macroalbuminuria was defined as AER ≥300 mg/24 h, and reduced eGFR was defined as estimated GFR <60 mL/min/1.73 m^2 on at least one occasion or progression to end-stage renal disease (9).

Retinopathy Assessments and Outcomes

Standardized stereoscopic seven-field fundus photographs were obtained every 6 months during DCCT and every 4th year (staggered from the start of the EDIC follow-up period) during EDIC. In addition, photographs were obtained in the full cohort at EDIC years 4 and 10. The photographs were graded centrally using the final Early Treatment Diabetic Retinopathy Study (ETDRS) severity grading scale. Graders were masked to treatment assignment and other risk factors (15).

Proliferative diabetic retinopathy (PDR) was defined by neovascularization observed on fundus photograph grading or evidence of scatter photocoagulation. Clinically significant macular edema (CSME) was defined based on fundus photography grading or the presence of focal photocoagulation scars. Ocular surgical interventions were self-reported at annual visits and captured based on structured interviews conducted by the study staff. Ocular surgery was defined as a composite outcome that included cataract extraction, vitrectomy, and/or retinal detachment surgery, glaucoma-related surgery (including laser treatment, filtering surgery, cyclocryotherapy, or other operative procedures to lower intraocular pressure), cornea or lens-related surgery (including corneal transplant or yttrium aluminum garnet posterior capsulotomy), or enucleation (10,16).

Neuropathy Assessments and Outcomes

Diabetic peripheral neuropathy (DPN) was assessed twice during the DCCT (baseline and 5 years) and once during EDIC (year 13/14). The primary DPN outcome was confirmed clinical neuropathy, defined as at least two abnormal findings among symptoms, sensory signs, or reflex changes consistent with a distal symmetrical polyneuropathy (assessed by a certified neurologist) plus nerve conduction study abnormalities involving two or more nerves among the median (motor and sensory), peroneal, and sural nerves (17). Cardiac autonomic neuropathy (CAN) was assessed at up to five time points during DCCT (baseline and years 2, 4, 6, and 8) and twice during EDIC (EDIC year 13/14 and EDIC year 16/17) using the R-R response to paced breathing, Valsalva maneuver, and postural change in blood pressure under standardized conditions. Presence of CAN was defined as either an R-R variation <15 or an R-R variation between 15 and 19.9 in combination with a Valsalva ratio ≤ 1.5 or a decrease of >10 mmHg in diastolic blood pressure during 10 min of standing (18).

Mortality

Deaths were reported to the Data Coordinating Center along with external documentation (if available) and were adjudicated by a within-study Mortality and Morbidity Review Committee masked to original DCCT treatment group assignment and glycemic levels (19).

Statistical Analysis

Discrete factors were described using percentages, while quantitative factors were described using medians (first and third quartiles).

Separately for age and duration of T1D, the associations with glycemia (as captured by the mean updated HbA_{1c}, a time-varying exposure) were assessed using separate Cox proportional hazards (PH) models for CVD, retinopathy, nephropathy, and mortality and using longitudinal logistic regression models with generalized estimating equations for neuropathy. The models are not adjusted for other covariates. Therefore, the additional years of age yielding the same increase in the risk of an outcome as a 1-percentage point increase in HbA_{1c} is assessed in a model that only includes HbA_{1c} and age. Likewise, the additional years of duration of T1D yielding the same increase in the risk of an outcome as a 1-percentage point increase in HbA_{1c} is assessed in a model that only includes HbA_{1c} and duration of T1D.

As an illustration, consider glycemia and age relative to the risk of CVD. The number of years of age (Δ) that provides the same increase in CVD risk as a 1-percentage point increase in mean updated HbA_{1c} (such as from 7% to 8%) is the ratio of the log HR for HbA_{1c} to the log HR for age in a Cox PH model for CVD including both factors. Likewise, the number of years of age that provides the same odds of DPN or CAN as a 1-percentage point increase in mean updated HbA_{1c} is the ratio of log odds ratio (OR) for HbA_{1c} to the log OR for age in the generalized estimating equation model for prevalent neuropathy over time. Note that the value Δ can also be interpreted as the equivalent number of years saved with a 1-unit (1%) lower HbA_{1c}. Similar considerations apply for duration of T1D calculations instead of age.

CIs and *z*-test values for Δ were obtained using the delta method. Note that $\Delta = 0$ when HbA_{1c} is not associated with the outcome (i.e., the numerator is zero), and Δ is not defined when age (or duration of T1D) is not associated with the outcome (i.e., the denominator is zero). Moreover, the parameter increases as the HR (or OR) for HbA_{1c} increases or as the HR (or OR) for age or duration of T1D decreases. Conversely, the parameter decreases as the HR (or OR) for HbA_{1c} decreases or as the HR (or OR) for age or duration of T1D increases.

Our goal is different from evaluating whether the mean HbA_{1c} moderates (enhances/reduces) the effect of age on outcomes. Instead, interaction terms between HbA_{1c} and age (used as quantitative variables) were included in the models to assess whether the equivalent

Table 1—Baseline characteristics and number of events (with rate per 1,000 individuals at risk for 1 year for time-to-event outcomes or percent out of the number of evaluations for longitudinal outcomes) among the 1,441 DCCT/EDIC participants

A. Baseline characteristics	
Group (% intensive)	49
Cohort (% primary)	50
Sex (% males)	53
Age (years)	27 (22, 32)
BMI (kg/m^2)	23 (21, 25)
Smoking (%)	19
Systolic blood pressure (mmHg)	114 (106, 122)
Diastolic blood pressure (mmHg)	72 (68, 80)
Pulse pressure (mmHg)	40 (34, 48)
Pulse rate (bpm)	76 (68, 84)
Total cholesterol (mg/dL)	174 (153, 197)
Triglycerides (mg/dL)	70 (55, 94)
HDL (mg/dL)	49 (42, 57)
LDL (mg/dL)	107 (91, 127)
Duration of diabetes (years)	4 (2, 9)
eGFR (mL/min/1.73 m^2)	125 (118, 134)
Log AER (mg/24 h)	2.4 (2.0, 2.9)
HbA_{1c} (%)	8.8 (7.8, 10.1)
HbA_{1c} (mmol/mol)	73 (62, 87)
B. Outcomes	
Any CVD	184 (5.2*)
MACE	88 (2.4*)
Macroalbuminuria	192 (5.0*)
Reduced eGFR	189 (4.9*)
PDR	379 (12*)
CSME	431 (14.5*)
Ocular surgery	281 (7.6*)
DPN	662 (16.9†)
CAN	1,199 (15.8†)
Mortality	152 (3.9*)

Baseline characteristics data are median (interquartile range) for quantitative variables and prevalence percentage for discrete variables. *Rate per 1,000 individuals at risk for 1 year. †Percent out of the number of evaluations ($N = 3,919$ for DPN, and $N = 7,574$ for CAN).

number of years of age differed by glycemic levels. If statistically significant, then the equivalent number of years of age are reported stratified by HbA_{1c} levels $<7.5\%$, between 7.5% (inclusive) and 8.5%, and $\geq 8.5\%$. Similar calculations were conducted for HbA_{1c} and duration of T1D.

We also assessed whether the results differed by the initial DCCT treatment group (intensive vs. conventional) assignment, which was addressed in two ways. The first approach was to assess whether the effect of the mean updated HbA_{1c} on the risk of outcomes differed between the original intensive group versus the conventional group by using an interaction term between mean updated HbA_{1c} and group. The second approach was to conduct calculations separately by the original DCCT group.

Given the exploratory nature of our analyses, the results were not adjusted for multiple testing, and *z*-test values >2 in absolute value (or equivalently two-sided *P* values <0.046) were considered nominally significant. However, to achieve significance at level 0.05 adjusting for the 10 tests (the number of outcomes) using the Holm procedure would require an absolute *z*-test value <2.81 in absolute value (or a two-sided *P* value <0.005) for the most significant test and smaller *z* values (larger *P* values) for the others.

RESULTS

The results reported in this study are based on the data sets described in our previous publications (8–10).

Detailed descriptions of the baseline characteristics of the DCCT cohort have been reported previously (14). Briefly, at baseline, 47% of the participants were women, median age was 27 years (first and third quartiles of 22 and 32 years, respectively), median duration of T1D was 5.6 years (2.2 and 9), median systolic blood pressure was 114 mmHg (106 and 122), and median diastolic blood pressure was 72 mmHg (68 and 80) (Table 1*A*).

During the combined DCCT/EDIC follow-up, among the 1,441 participants, there were 184 any-CVD events and 88 MACE, 192 macroalbuminuria and 189 reduced eGFR events, 379 PDR and 431 CSME events, 281 ocular surgeries, and 152 deaths. There were 662 evaluations (of 3,919 total evaluations) positive for DPN and 1,199 evaluations (of 7,574 total evaluations) positive for CAN (Table 1*B*).

Table 2 reports the equivalent number of years of age and of T1D duration that provide the same increase in risk as a 1-percentage point increase in the mean updated HbA_{1c} (such as from 7 to 8%). The log (HR) for HbA_{1c} was 0.403 and for age was 0.094. Thus, an additional $\Delta = 0.403/0.094 = 4.3$ years of age would provide the same increase in CVD risk as a 1-percentage point increase in mean updated HbA_{1c}. The test of the hypothesis $\Delta = 0$ yields a *z*-test value of 5.44 (or equivalently, a *P* value <0.0001) that is highly significant. For most of the outcomes considered, a 1-percentage point increase in HbA_{1c} corresponded to a substantial number of years of age or duration of T1D. The equivalent years of age are slightly lower than the equivalent years of duration for any CVD, MACE, and reduced eGFR and higher for CSME, ocular surgery, DPN, and CAN. For mortality, a 1-percentage point increase in mean updated HbA_{1c} (such as from 7 to 8%) resulted in the same increase in the risk as an increase of 12.9 years of age.

Additional models added an interaction term between HbA_{1c} and age to the models in Table 2. Interaction *z*-test values >2 in absolute value were observed for interaction terms between mean updated HbA_{1c} and age for reduced eGFR ($z = -4.916$) and CAN ($z = 3.040$) and between mean updated HbA_{1c} and duration of T1D for PDR ($z = 2.216$) and CSME ($z = 2.081$). The equivalent numbers of years of age and T1D duration for a 1-percentage point higher mean updated HbA_{1c} stratified by HbA_{1c} levels $<7.5\%$, between 7.5% (inclusive) and 8.5%, and $\geq 8.5\%$ are reported in Table 3. The equivalent number of years of age increased as the HbA_{1c} level increased for both reduced eGFR and CAN (Table 3*A*). The equivalent number of years of T1D duration decreased for PDR as HbA_{1c} increased, while for CSME, it was lower for $HbA_{1c} \geq 8.5\%$ than for HbA_{1c} levels $<7.5\%$ and between 7.5% and 8.5%.

We did not find evidence of differences in the relationship between mean updated HbA_{1c} and age/duration of T1D between the two initial DCCT treatment groups (intensive vs. conventional). For

Table 2—The number of years (Δ) of either age or duration of T1D that provides the same ratio of risk of outcomes (OR for DPN and CAN and HR for others) as does the mean updated HbA_{1c} (per 1-percentage point increase, such as from 7% to 8%)

	Age						Duration of T1D					
	Coefficient HbA_{1c}	Coefficient age	Δ*	LL	UL	*z*	Coefficient HbA_{1c}	Coefficient duration	Δ†	LL	UL	*z*
Any CVD	0.403	0.094	4.3	2.7	5.8	5.4	0.350	0.062	5.6	2.3	9.0	3.3
MACE	0.517	0.113	4.6	2.7	6.5	4.7	0.462	0.073	6.4	1.8	10.9	2.8
Macroalbuminuria							0.912	0.060	15.2	6.6	23.8	3.5
Reduced eGFR	0.854	0.071	12.1	8.3	15.9	6.3	0.382	0.020	18.0	4.3	31.7	2.6
PDR							0.912	0.143	6.4	5.3	7.4	11.6
CSME	0.641	0.034	18.9	11.6	26.2	5.1	0.663	0.093	7.1	5.4	8.8	8.0
Ocular surgery	0.718	0.063	11.4	8.2	14.6	6.9	0.698	0.096	7.3	5.1	9.4	6.6
DPN	0.523	0.066	7.9	5.8	9.9	7.5	0.468	0.084	5.0	3.7	6.3	7.4
CAN	0.355	0.072	5.0	3.5	6.4	6.8	0.338	0.082	4.1	2.8	5.5	5.8
Mortality	0.617	0.048	12.9	6.6	19.3	4.0						

The *z* values correspond to a test of the null hypothesis $\Delta = 0$. Only results with *z*-test values >2 in absolute value (or equivalently, a two-sided *P* value <0.046) are presented. Coefficient, log OR for DPN and CAN and log HR for others; LL, lower limit for 95% CIs; UL, upper limit for 95% CIs. *The additional years of age equivalent to a 1-percentage point increase in HbA_{1c} Δ is the ratio of the coefficient for HbA_{1c} to the coefficient for age. For example, for "Any CVD": $4.3 = 0.403/0.094$. †Likewise, the additional years of duration of T1D equivalent to a 1-percentage point increase in HbA_{1c} Δ is the ratio of the coefficient for HbA_{1c} to the coefficient for duration of T1D. For example, for "Any CVD": $5.6 = 0.350/0.062$.

Table 3—The number of years (Δ) of age (*A*) or duration of T1D (*B*) that provides the same ratio of risk of outcomes (OR for CAN and HR for others) as does the mean updated HbA_{1c} stratified by HbA_{1c} levels <7.5%, ≥7.5% and <8.5%, and ≥8.5%

	Δ	LL	UL	*z*
A. The additional years of age equivalent to a 1-percentage point increase in HbA_{1c}				
Reduced eGFR				
Overall	12.1	8.3	15.9	6.29
HbA_{1c} <7.5%	−0.7	−5.3	4.0	0.28
7.5% ≤ HbA_{1c} < 8.5%	10.4	2.5	18.3	2.57
HbA_{1c} ≥8.5%	25.3	8.6	42.0	2.98
CAN				
Overall	5.0	3.5	6.4	6.75
HbA_{1c} <7.5%	1.2	−2.7	5.2	0.61
7.5% ≤ HbA_{1c} < 8.5%	4.2	−1.2	9.5	1.51
HbA_{1c} ≥8.5%	6.2	3.1	9.3	3.95
B. The additional years' duration of T1D equivalent to a 1-percentage point increase in HbA_{1c}				
PDR				
Overall	6.4	5.3	7.4	11.62
HbA_{1c} <7.5%	11.8	1.7	22.0	2.29
7.5% ≤ HbA_{1c} < 8.5%	10.4	4.8	16.1	3.59
HbA_{1c} ≥8.5%	5.4	4.2	6.6	8.79
CSME				
Overall	7.1	5.4	8.8	8.03
HbA_{1c} <7.5%	10.6	0.2	21.0	1.99
7.5% ≤ HbA_{1c} < 8.5%	17.2	6.9	27.6	3.26
HbA_{1c} ≥8.5%	6.3	4.2	8.4	5.93

The *z* values correspond to a test of the null hypothesis $\Delta = 0$. Only results for outcomes with *z*-test values for interactions >2 in absolute value (or equivalently, a two-sided *P* value <0.046) for an interaction term between the mean updated HbA_{1c} and age (*A*) and duration of T1D (*B*) are shown. HbA_{1c} values of 7.5% and 8.5% correspond to 58 mmol/mol and 69 mmol/mol, respectively. LL, lower limit for 95% CIs; UL, upper limit for 95% CIs.

example, for any CVD, the interaction between mean updated HbA_{1c} and group was not statistically significant ($P = 0.3034$), and Δ was 4.5 in the conventional group and 4.1 in the intensive group. Likewise, for MACE, the interaction between mean updated HbA_{1c} and group was not statistically significant ($P = 0.3233$), and Δ was 4.7 in the conventional group and 4.7 in the intensive group.

CONCLUSIONS

Age and duration of diabetes are known but unmodifiable risk factors for microvascular and cardiovascular outcomes and mortality in T1D. In this study, we express the direct effect of glycemic exposure in terms of equivalent years of age and duration of T1D in a large and carefully studied cohort of individuals with T1D.

The number of years of age (Δ) that provides an HR for CSME equivalent to that of a 1-percentage point increase in HbA_{1c} (such as from 7 to 8%) was large (18.9 years). As a ratio parameter, large Δ values can occur either due to a large numerator (HR for HbA_{1c}) or a small denominator (HR for age). For CSME, the effect (i.e., the HR) for HbA_{1c} was similar to that for ocular surgery, but the effect for age was much smaller. The HR for the association between HbA_{1c} and the risk of PDR was similar to that for CSME. However, the association between age and the risk of PDR was not statistically significant, while the association with the risk of CSME was highly significant. Note that the risk of macroalbuminuria was not associated with age when adjusted for the mean updated HbA_{1c}, and mortality was not associated with duration of T1D when adjusted for the mean updated HbA_{1c}.

Our approach can be used for other risk models for CVD, such as the Steno Type 1 risk engine, in which CVD was a composite outcome defined as ischemic heart disease, ischemic stroke, heart failure, and peripheral artery disease (20). The Steno model also included sex, diabetes duration, systolic blood pressure, LDL, albuminuria, eGFR, smoking, and exercise. Using our approach to the Steno model, a 1-percentage point increase in HbA_{1c} is equivalent to ∼3.3 years of age in terms of risk of CVD, qualitatively similar to our estimate of 4.3 in the DCCT/EDIC study.

Diabetes has been proposed as a potential cause of accelerated aging (21), with genetic alterations (e.g., leukocyte DNA methylation [22]) and premature cell senescence (e.g., endothelial progenitor cells and proximal tubular cells [23]) as potential pathways. Our approach allows for the quantification of premature aging by expressing the risk of outcomes in terms of equivalent years of age or duration of diabetes. Since the DCCT/EDIC cohort only includes individuals with T1D and does not have a comparison group of individuals without diabetes, we illustrate this approach using results from the Framingham Study. The Framingham risk score for CVD uses a CVD composite outcome defined as coronary heart disease, cerebrovascular events, peripheral artery disease, and heart failure (24). Furthermore, the Framingham model provides risk estimates separately for women and men based on log transformed values for age, total cholesterol, HDL cholesterol, systolic blood pressure (separately for treated and not treated), smoking (yes/no), and diabetes (yes/no, T1D, and type 2 diabetes combined). Since age was evaluated on the log scale in the

Framingham model, our approach for estimating the number of years age equivalent to diabetes present versus not present is expressed as a fold change: 1.35-fold for women and 1.21-fold for men. The average age during follow-up in the DCCT/EDIC cohort was 39.2 years, so that the additional risk of CVD between those with and without diabetes corresponds to ~13.6 (= 39.2 × 0.35) years of age for women and 8.1 (= 39.2 × 0.21) years of age for men. Of note, in the DCCT/EDIC cohort, the 13.6 and 8.1 years of age correspond to ~3.2% (= 13.6/4.29) higher HbA_{1c} (such as from 5% to 8.2%) and 1.9% (= 8.1/4.29) higher HbA_{1c} (such as from 5% to 6.9%), respectively.

We estimated the number of years of age and duration of T1D that yield the same increase in risk as a 1-percentage point increase in mean HbA_{1c} using a Cox PH model, which is a relative risk model. However, the approach can be used for virtually any regression model. For example, using an Aalen additive risk model for any CVD yielded $\Delta = 4.2$ (95% CI 2.7–5.7), very similar to $\Delta = 4.3$ (95% CI 2.7–5.8) using the Cox PH model.

As with results from any clinical study, our findings apply most directly to populations with similar risk sociodemographic profiles, treatments, and definitions and assessments of outcomes. Extrapolation to different populations requires strong and mostly untestable assumptions. Because of the rigorous and standardized assessments of putative risk factors and outcomes for nearly three decades, the fact that diabetes care has been provided by community practitioners for >20 years, and the results did not differ for former intensive and conventional therapy participants, we believe our findings are generalizable to other similar populations with T1D.

A limitation of our study is that current cardiorenal-protective agents were either unavailable (statins and angiotensin receptor blockers) or not prescribed by protocol (ACE inhibitors) during the DCCT. However, these agents have been available and their use has increased during EDIC (e.g., to 43% and 59% use of ACE inhibitors and lipid-lowering medication, respectively, at 25 years from DCCT baseline). Since most of the outcomes occurred during EDIC (e.g., 165 out of the 184 any-CVD events and all 88 MACE), when these agents were available to our participants, our findings are based on a cohort of individuals with T1D receiving standard diabetes care.

These analyses demonstrate that the effect of average glycemia, as measured by a 1-percentage point increase in mean undated HbA_{1c}, can be expressed in terms of additional years of age or duration of T1D that yield the same risk of microvascular and cardiovascular complications and mortality. The results provide a clinically relevant interpretation of the burden of glycemia on advanced complications that may prove more intuitive to health care providers and individuals with T1D and therefore reinforce their efforts to strive for optimal glycemic control.

Funding. The DCCT/EDIC has been supported by cooperative agreement grants (1982–1993, 2012–2017, and 2017–2022) and contracts (1982–2012) with the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (grants U01 DK094176 and U01 DK094157) and through support by the National Eye Institute, the National Institute of Neurological Disorders and Stroke, the General Clinical Research Center Program (1993–2007), and Clinical and Translational Science Center Program (2006–present) (Bethesda, MD). Industry contributors have had no role in the DCCT/EDIC study but have provided free or discounted supplies or equipment to support participants' adherence to the study: Abbott Diabetes Care (Alameda, CA), Animas Corporation (West Chester, PA), Bayer Diabetes Care (Tarrytown, NY), Becton Dickinson (Franklin Lakes, NJ), Eli Lilly and Company (Indianapolis, IN), Extend Nutrition (St. Louis, MO), Insulet Corporation (Bedford, MA), LifeScan, Inc. (Milpitas, CA), Medtronic Diabetes (Minneapolis, MN), Nipro Home Diagnostics, Inc. (Fort Lauderdale, FL), Nova Diabetes Care (Billerica, MA), Omron (Shelton, CT), Perrigo Diabetes Care (Allegan, MI), Roche Diabetes Care (Indianapolis, IN), and Sanofi U.S. (Bridgewater, NJ).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. I.B. wrote the initial draft of the manuscript with assistance from J.M.L. and conducted all analyses. B.H.B., D.S., W.S., J.I.M., R.P.-B., G.M.L., P.L., V.R.T., A.W., and W.H.H. contributed to the specification of the analyses and critically reviewed and edited the manuscript. I.B. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. American Diabetes Association. 11. Microvascular complications and foot care: *Standards of Medical Care in Diabetes—2019*. Diabetes Care 2019;42(Suppl. 1):S124–S138
2. Orchard TJ, Costacou T, Kretowski A, Nesto RW. Type 1 diabetes and coronary artery disease. Diabetes Care 2006;29:2528–2538
3. Livingstone SJ, Looker HC, Hothersall EJ, et al. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. PLoS Med 2012;9:e1001321
4. Lind M, Svensson AM, Rosengren A. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med 2015;372:880–881
5. Rawshani A, Rawshani A, Gudbjörnsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med 2017;377:300–301
6. Miller RG, Mahajan HD, Costacou T, Sekikawa A, Anderson SJ, Orchard TJ. A contemporary estimate of total mortality and cardiovascular disease risk in young adults with type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes Care 2016;39:2296–2303
7. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. Diabetes Care 2016;39:1378–1383
8. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Risk factors for cardiovascular disease in type 1 diabetes. Diabetes 2016;65:1370–1379
9. Perkins BA, Bebu I, de Boer IH, et al.; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Risk factors for kidney disease in type 1 diabetes. Diabetes Care 2019;42:883–890
10. Hainsworth DP, Bebu I, Aiello LP, et al.; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Risk factors for retinopathy in type 1 diabetes: the DCCT/EDIC study. Diabetes Care 2019;42:875–882
11. Lachin JM, Orchard TJ, Nathan DM; DCCT/EDIC Research Group. Update on cardiovascular outcomes at 30 years of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. Diabetes Care 2014;37:39–43
12. The DCCT Research Group. The Diabetes Control and Complications Trial (DCCT). Design and methodologic considerations for the feasibility phase. Diabetes 1986;35:530–545
13. The DCCT/EDIC Research Group. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care 1999;22:99–111
14. Writing Group for the DCCT/EDIC Research Group. Coprogression of cardiovascular risk factors in type 1 diabetes during 30 years of follow-up in the DCCT/EDIC study. Diabetes Care 2016;39:1621–1630
15. Lachin JM, White NH, Hainsworth DP, Sun W, Cleary PA, Nathan DM; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. Diabetes 2015;64:631–642
16. Aiello LP, Sun W, Das A, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and ocular surgery in type 1 diabetes. N Engl J Med 2015;372:1722–1733
17. Martin CL, Albers JW, Pop-Busui R; DCCT/EDIC Research Group. Neuropathy and related findings

in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. Diabetes Care 2014; 37:31–38
18. Pop-Busui R, Braffett BH, Zinman B, et al.; DCCT/EDIC Research Group. Cardiovascular autonomic neuropathy and cardiovascular outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. Diabetes Care 2017; 40:94–100
19. Orchard TJ, Nathan DM, Zinman B, et al.; Writing Group for the DCCT/EDIC Research Group. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA 2015;313:45–53
20. Vistisen D, Andersen GS, Hansen CS, et al. Prediction of first cardiovascular disease event in type 1 diabetes mellitus: the Steno type 1 risk engine. Circulation 2016;133:1058–1066
21. Cerami A. Hypothesis. Glucose as a mediator of aging. J Am Geriatr Soc 1985;33:626–634
22. Toperoff G, Kark JD, Aran D, et al. Premature aging of leukocyte DNA methylation is associated with type 2 diabetes prevalence. Clin Epigenetics 2015;7:35
23. Burton DGA, Faragher RGA. Obesity and type-2 diabetes as inducers of premature cellular senescence and ageing. Biogerontology 2018;19:447–459
24. D'Agostino RBS Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–753